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Collisions and coalescence in droplet streams for the production of freeze-dried powders

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ABSTRACT

Streams of mono-disperse micro-droplets with diameters ranging from about 20 μm to 100 μm were produced from diluted aqueous solutions containing carbohydrates and proteins using a pinhole type piezoelectric generator with either a 20 μm or a 50 μm single-orifice diaphragm. Image sequences indicating droplet size, velocity, inter-droplet spacing at various distances from the nozzles as well as collision events and coalescence were recorded using a high-speed camera and analysed quantitatively. The size-dependent gradual deceleration of the droplets is superimposed by small scale random movements, which equally affect both large and small droplets and lead to early contacts and coalescence. The loss of mono-dispersity can be reduced by quick cooling since both the nucleation rate and the freezing rate of micro-droplets are extremely dependent upon the temperature of their gaseous environment.

1. Introduction

Recent years have witnessed a growing interest in spray freeze-drying processes in particular for the formulation of peptide and protein drugs [1–4]. Contrary to the standard spray drying, spray freeze-drying is mild to peptides and proteins due to the presence of the lyophilisation step, which allows the conservation of the pharmacological activity of such molecules. However, a common drawback of the spray-freeze drying process is the relatively broad poly-dispersity of the resulting particles, which can be remedied through the optimization of the droplet streaming [5].

The first indispensible step towards manufacturing lyophilisate powders with optimally uniform spherical particles involves the generation of the small droplets of equal size [6]. Such spherolyophilisate particles are formed by freezing the droplet stream during sedimentation in a gaseous environment at a temperature below 220 K, and the subsequent lyophilisation of these droplets. Unlike in spray-drying, the freezing of the sprayed droplets and the subsequent sublimation can ideally lead to the formation of particles with a size corresponding to that of the initial droplets.

Spray freeze-drying provides a particularly intriguing platform for the preparation of the small and uniformly spherical low-density particles for the pulmonary administration of peptides and protein drugs [7–9]. Though generating mono-disperse droplet streams followed by their lyophilisation offers the possibility to produce very uniform particulate lyophilisates, collision of the droplets prior to congelation can lead to coalescence and the consequent growth of the particle size distribution and the poly-dispersity of the prepared particles. Several methods have been proposed to enable the visualization of this phenomenon. These techniques have been previously compared and allow the unspecific characterization of the droplet stream [5]. The present study has been a contribution to a project with the objective to produce powder aerosols with uniform spherical lyophilized particles.

Aqueous solutions containing less than 10% of solids can be used to produce mono-disperse streams of droplets with diameters below 20 μm, which are promising for the production of uniform lyophilized particles with low density and enhanced pulmonary deposition characteristics. The production of small and precisely sized droplets has been perfected for ink-jet printing and dispensing of analytical reagents. Droplets in fast-moving streams are subject to two kinds of aerodynamic interactions: a gradual deceleration, which affects the entire flow, and localized disturbances by which single or short sequences of droplets are accelerated in various directions [5]. This is irrelevant for printing, where trajectories are short, but if tightly spaced droplets collide in flight before

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Table 1
Statistics of primary droplets, deceleration constants and collision distances.

Observations	Droplet generator pinhole diameter [μm]					
	20			50		
	Mean	SD	*N*	Mean	SD	*N*
Mean projection area [pixels]	17.0	2.29	34	40.1	2.37	24
Apparent initial diameter d_0 (μm)	51.8	2.5	108	79.4	3.01	106
Centre–centre spaces Δ_0 (μm)	129.2	14.93	105	171.9	9.73	102
Initial velocity u_0 (m/s)	6.75	0.11	31	8.67	0.04	21
Deceleration constant k (1/mm)	0.0086			0.0038		
Collision distance L_c (mm), expected	113			183		
Collision distance L_c (mm), observed	10			20		

they are frozen, they coalesce, and the initially uniform small size is lost. The resulting heterogeneity may affect pulmonary deposition patterns and increase the variability component of bioavailability attributable to the drug product. The quantitative study of droplet collision patterns elucidates the underlying mechanisms and has contributed to the development of efficient measures to reduce the incidence or eliminate early collisions in droplet streams [10].

The problem of size uniformity has been solved for granulates with particles in the millimetre range, which are produced on a large scale in the fertilizer, detergent and explosives industries by spray-congealing and drying drops of concentrated solutions or slurries using the prilling technology [11]. Droplets with diameters of less than about 50 μm ejected in streams from piezoelectric generators are much more susceptible to aerodynamic interference because of their low inertia and because their initial velocity is much higher than their terminal sedimentation rate. Ultimately, aerodynamic braking will always lead to collisions, but if the droplets are already frozen, the contact does not change the particle size distribution. On the other hand, the high specific surface area and low thermal inertia of small droplets facilitate freezing and the small globules can be dried efficiently either under vacuum or in a dry gas flow. Quantitative image analysis of fast droplet streams contributes to understanding the causes and mechanisms leading to collisions, particularly the contribution of random jitter to early droplet collisions [5]. The images were taken at ambient temperature, where the density of the gaseous boundary layer is much lower while the velocity of the gas jet and its viscosity are higher than under freezing conditions. Nevertheless, the quantitative analysis indicates a direction where a solution of the coalescence problem can be found.

2. Experimental methods

2.1. Droplet generation

Streams of mono-disperse micro-droplets were generated using a piezoelectric generator (MTG-01G1; FMP Technology GmbH, D-Erlangen) actuated at 48 kHz with a rectangular signal and equipped with single 20 μm or 50 μm pinhole diaphragms. Aqueous solutions containing 5% (w/w) mannitol, 1% (w/w) lysozyme and 0.1% (w/w) maltodextrin with a viscosity ν 1.42 mPa s, surface tension σ 73.5 mN/m and density ρ 1.02 g/cm^3 were supplied at a feed pressure of 150 kPa. Pressure waves travelling down the barrel eject droplets with diameters somewhat greater than the pinholes (Table 1).

2.2. Imaging and image analysis

Images were taken in each recording at representative down-track distances L from the orifice, using a Photron FastCam SA4 camera with back light illumination by a Seoul Z-P4 light emitting diode. Images were viewed using the Photron Fast Cam Viewer software version 3.2.3 by Photron (Europe) Limited, West Wycombe, UK. In each series 1500 frames with 64 × 400 square pixels and a resolution of 11.9 × 11.9 μm were taken at a rate of 60,000 per second with an integration time of 2 μs. The frames are thus 4.76 mm high and 0.76 mm wide. Numerical values of the bit counts and coordinates of droplets were determined using the NIH open

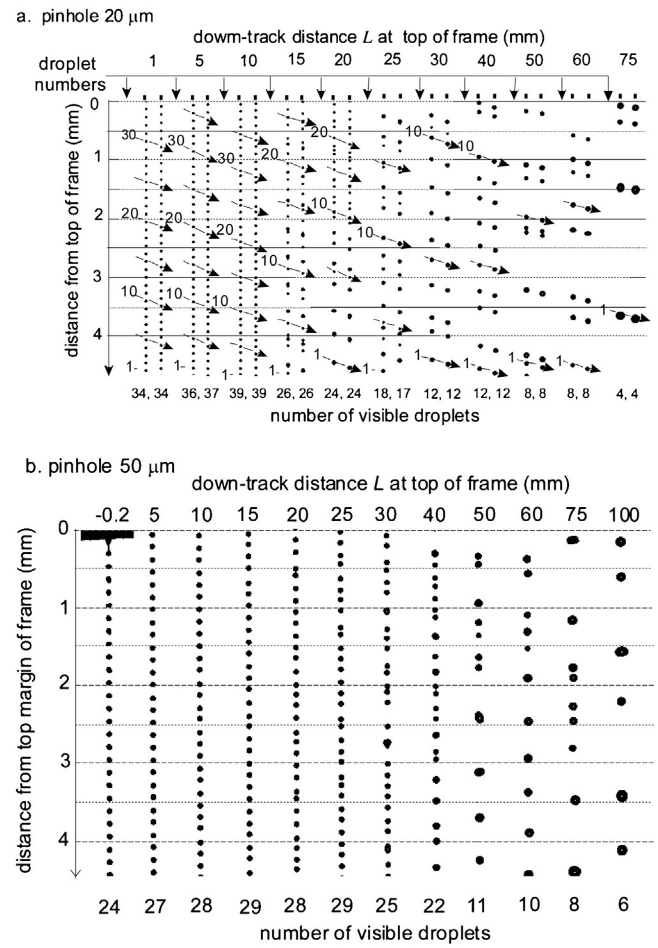

Fig. 1. Droplet spacing and collision patterns are given exemplarily for 20 μm (a) and 50 μm (b) pinholes.

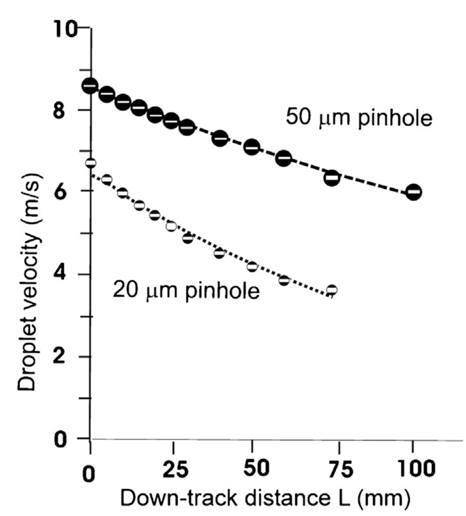

Fig. 2. Average velocities of droplets at different down-track distances are given in dependency of the pinhole diameter. The width of horizontal bars corresponds to one standard deviation of scatter.